UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/817,058	04/02/2004	John E. Baker	BA-32448(1)	2664

22202 7590 10/11/2005

WHYTE HIRSCHBOECK DUDEK S C
555 EAST WELLS STREET
SUITE 1900
MILWAUKEE, WI 53202

EXAMINER	
MAYER, SUZANNE MARIE	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/817,058	BAKER ET AL.	
	Examiner	Art Unit	
	Suzanne M. Mayer, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23-31 and 47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21,23-31 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8-5-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims Status

1. Claims 22 and 32-46 have been cancelled by Applicants. Claim 47 has been added. The amendment to the claims and the Declaration under 37 C.F.R. 1.131 are acknowledged and accepted. Thus claims 1-21, 23-31 and 47 are pending.

Withdrawal of Finality of Previous Office action

2. The Finality of the previous Office action from May 5, 2005 is hereby withdrawn in view of newly acquired prior art. See below.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on August ~~17~~ 5, 2005 has been considered by the examiner. See signed and attached PTO-1449.

Maintained Objections and Rejections

4. All the rejections from the previous Office action are hereby withdrawn in view of the 37 C.F.R. 1.131 Declaration submitted by Applicant which overcomes the 35 U.S.C 102 (a and e) rejections and the 35 U.S.C. 103(a) rejection.

New Objections and Rejections

Specification

5. The disclosure is objected to because of the following minor informalities: on page 9, line 10 of the specification, a does of 50 U/kg is stated as being equivalent to 500 ng/kg or 0.5 mg/kg. Clearly, this is an inadvertent typographical error and should read as 0.5 μg/kg.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 47 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim limitation of reducing the effects of myocardial ischemia in a patent by administering EPO, will not work for reducing effects of said ischemia in just any patient. It must be in a patient in need thereof.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to the prevention of myocardial ischemia by administering EPO. However, the methods described in the specification and the examples they are drawn to only indicate lessening the effects of myocardial ischemia by administering EPO. The complete abolition of myocardial ischemia is not described in such a way that actually shows that applicant were actually capable of doing so, and the prior art teaches that it is nearly impossible to completely prevent myocardial ischemia and a skilled artisan would recognize this deficiency in teaching in the specification. Thus, it is apparent that applicants were not in possession of this aspect of their claimed invention at the time of filing.

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-21, 23-31 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Brines et al. (US 6,531,121).

Brines' et al. teach methods of treating or preventing ischemia in patients suffering from various ischemic events (e.g. myocardial or neural ischemia (see Examples 3 and 5), and also to preserve and treat organs used in transplants in order to prevent or treat an ischemic event in an organ transplant recipient patient. Both methods achieve these results through the use and/or administration of erythropoietin (EPO) in specific doses.

Brines et al. teach a thorough background regarding EPO and the rational and reasons for the success of their invention. For many years, the only clear physiological role of erythropoietin (EPO) was thought to be its control of the production of red blood cells. However, several lines of evidence suggested that EPO, a member of the cytokine superfamily, performed other important physiologic functions which were mediated through interaction with the erythropoietin receptor (EPO-R). These actions included mitogenesis, modulation of calcium influx into smooth muscle cells and neural cells, and effects on intermediary metabolism. It was believed that EPO would provide compensatory responses that would serve to improve hypoxic cellular microenvironments. (A hypoxic environment is defined as an environment where oxygen is limited or at a lower concentration than normal. A hypoxic environment is induced in tissues or organs whenever an ischemic event takes place in said tissue or organs.)

Thus, Brines et al. teach that their invention is the identification of tissues and organs where EPO can migrate across tissue barriers that were previously thought impenetrable to EPO, and therefore identifying new methods of treating patients and/or

organs prone to ischemic damage by using EPO. The following is a summary of their inventions: EPO can be successfully administered or perfused in any organ and/or tissue which has erythropoietin responsive cells (column 11, lines 33-50) such as retinas, lungs, kidneys, neurons or heart (column 4, lines 13-25).

Thus, Brines et al. have identified several tissues and/or organs which previously were thought not to be responsive to EPO, such as the brain, retina's of the eyes and the heart. As way of a very specific example (see Example 3, and Figure 2), Brines et al. teach a method of protecting the myocardium from ischemic injury by administering 5000 U/kg erythropoietin (EPO) 24 hours prior and again immediately before an induced ischemic event to the heart. The results were measured by measuring the pressure of the left ventricular pressure of the heart (see Figure 2). The results showed significantly less damage to the heart which was protected/treated with EPO as compared to the heart which was treated/protected with saline as the control.

When the invention is practiced by systemic administration, Brines' et al. teach the following concentrations of EPO to be administered to a subject and the resulting blood/serum concentration level achieved when said concentrations of EPO are administered, and finally, the time in which to expect the EPO blood/serum concentration to be achieved.

> In a preferred embodiment, an erythropoietin may be administered systemically at a dosage between 100 nanograms to about 50 micrograms per kg body weight, preferably about 20 micrograms to about 50 micrograms per kg-body weight. In the instance where an erythropoietic erythropoietin is used, the range may preferably be about 20 micrograms to about 50 micrograms per kg body weight. This effective dose should be sufficient to achieve serum levels of erythropoietin from about 10 picograms to about 1000 nanograms per ml of serum after erythropoietin administration. Such serum levels may be achieved at

about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 hours post-administration (column 12, lines 19-39).

For other routes of administration, such as by use of a perfusate, injection into an organ, or other local administration, a pharmaceutical composition will be provided which results in similar levels of an erythropoietin as described above. A level of about 10 pg/ml to about 1000 ng/ml is desired (column 12, lines 56-61).

In order to further understand the inventions taught by Brines' et al., as well as the limitations of the claims in the instant application, it is necessary to understand that one unit (U) of EPO, with a MW of approximately 34,000 Da, is equivalent to 10 ng of protein and thus one mg of protein is equal to 100,000 U (column 11, lines 14-16). Thus based upon the fact that 1 U EPO = 10 ng (and 10^{-5} mg); then the Brines' et al. preferred embodiment for systemically (parenterally) administering a dosage between 100 nanograms to about 50 micrograms per kg body weight, is equal to 10-5000 U/kg. Likewise, Brines' et al. preferable dosage is from about 20-50 μg/kg which is equal to 2000-5000 U/kg (Both of these doses encompass the dosage range in instant claims 1, 2, 5-7, 24, 26, 28, 30 and 31).

Also, central to both Brines' et al. invention, and also the claim limitation of the instant application, is the blood/serum concentration achieved after administration of EPO has occurred. Thus, also based on the above conversion numbers (1 U EPO = 10 ng (and/or 10^{-5} mg), Brines' et al. teach that the achieved EPO serum/blood concentration will be in the range of 10 picograms to 1000 nanograms, which is equal to .001-10 u/ml (based upon administration of 2000-5000 U/kg EPO). This concentration as taught by Brines et al. specifically spans the range of instant claims 2-5, 7, 19, 23, 24, 26, 28 and 31. This EPO serum concentration level is achieved in about 1-10

hours when systemic administration is used (parenterally). It should also be noted, that Brines et al. also teach that in terms of other local administration routes, such as local administration or perusing an organ with the same amount of EPO, that the same EPO blood/serum concentration is achieved.

Therefore, Brines' et al. teach the ranges of EPO to be administered and the blood concentration achieved after administration that will prevent or treat an ischemic event, specifically in the heart. Brines' et al. teach a greater range (10-5000 versus 50-5000 U/kg) as well as a greater range expected for the EPO blood/serum concentration (.001-10 versus 0.5-10 U/ml) as compared to the instant claim limitations which anticipates the majority of the limitations set forth in the instant claims.

11. Claims 3-5, 17, 19-23, 29-26, 28 and 30 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Brines et al. (US 6,531,121).

The teachings of Brines et al. is described in detail above. Brines et al., however, do not explicitly teach a specific the exact range that spans the length of the time of administration of EPO (e.g. continuous administration for 1-35 minutes; claim 3) and the time in which the desired EPO blood levels are achieved (claims 4, 24, 26, 28,30 and 47).

However, Brines et al. *do* teach that administration of EPO can be performed by various modes that will slowly and continuously administer EPO such as transdermal patches or osmotic pump (see column 15 and lines 40-43), in controlled release

systems well known to those in the art (see column 15, lines 63-67) or by suppositories, which will release EPO slowly and continuously over a period of time (see column 15, lines 13-15). Thus Brines et al. teach methods to deliver EPO to a mammal in a slow and continuous manner by methods that are very well known to those in the art. (This limitation of continuous administration for 1-35 minutes is addressed in claim 3).

The instant claim limitations are necessarily and *inherently* met by the teachings of Brines et al. because *both* methods are the same in regards to the same EPO U/kg range that is administered to a mammal which results in the *same* EPO blood concentration range, with the only difference being the claimed amount of time in which that concentration is achieved. Furthermore, since Brines et al. teach the same dosage range, the same administration routes (e.g. slow release methods, or intravenous routes) and the same outcome of the administration (desired EPO blood levels) as that of the instant application; then inherently they will achieve the same results in the same amount of time. Feit et al. (2003, J. Pat. Trade. Off. Soc., Vol. 85, No. 1, pages 5-21) teach three criteria for inherency. (1) The most important criterion is certainty. Citing *In re Tomlinson* and *In re Zierden*, Feit et al. state that certainty is established when the reference process necessarily **results** in the claimed process as opposed to a **possibility.** (2) The second criterion is chronology; it will always happen. Feit et al. state that the chronological test is forward chronology. Citing *Eli Lilly and Co. v Barr Laboratories, Inc.*, Feit et al. argue that the claimed result must always be obtained based upon the prior art method. 3) The third criterion is the legal standard. Feit et al., citing *Continental Can,* state that the legal standard is whether the missing descriptive

material would be so recognized by a person of ordinary skill in the art as necessarily present in the thing. Thus, the examiner asserts that there is nothing in the claimed invention/claims which patentably differentiates the subject matter from that of Brines et al.

10. The examiner wishes to specifically address the limitations of certain claims.

In claim 6, it was not understood what the quoted value "100 times the a normal level" in regards to level of EPO in a patient after administration of said EPO meant. Upon looking to the specification for guidance, the examiner was not able to find a definition anywhere, only an alternative recitation on p. 9-10 where the amount that was administered was, "effective to increase the blood level of EPO in a patient to about 100 times, preferably to about 500 times, above normal EPO blood levels, ***or*** an EPO blood level of about 100-5000 u/ml....". Therefore the examiner had to rely upon the definition that EPO blood levels that are 100-500 above the normal level is equal to 100-5000 u/ml. In view of this interpretation, the serum concentration levels taught by Brines et al. anticipate this claim.

The limitations set forth in claims 12-16, which are drawn to what causes the myocardial ischemic event, the methods of Brines' et al. inherently meet these claims. Because the method of Brines' et al. teaches the concentration, dosage of EPO to treat or prevent an ischemic event, particularly in the heart or brain (see Examples 3 and 5), then regardless of the cause of the ischemic event, the method in treating or preventing said ischemic event has already by been taught.

The limitation of claims 25 and 27 are drawn to methods of reducing myocardial ischemia in a patient by administering and effective amount of EPO to a patient so as to activate a protein kinase to prevent or reduce ischemic injury (claim 25) and activate a potassium channel to prevent or reduce the ischemic injury (claim 27). The limitations of what EPO does in the patients body in order to prevent an ischemic attack will be and is an inherent characteristic of EPO. Regardless if it is stated or not by Brines et al., inherently, administration of EPO as taught by Brines et al. will activate potassium channels and protein kinases because these are properties and functions of EPO, not of the claimed methods.

Brines' et al. also teach that they have discovered that organs and other bodily parts isolated from a mammalian body, such as those intended for transplant, are benefited by exposure to an erythropoietin (see column 2, lines 40-44). The following are examples of the invention taught by Brines' et al. which utilizes EPO concentrations for organ perfusion or storage/treatment of organs prior to transplantation as a solution comprising 1 – 25 U/ml (see column 16, lines 48-60).

> In the practice of another embodiment of the invention, various organs were planned to be harvested from a victim of an automobile accident for transplant

> into a number of recipients, some of which required transport for an extended distance and period of time. Prior to organ harvesting, the victim was infused with a pharmaceutical composition comprising an erythropoietin as described herein. Harvested organs for shipment were perfused with a perfusate containing erythropoietin as described herein, and stored in a bath comprising erythropoietin. Certain organs were continuously perfused with a pulsatile perfusion device, utilizing a perfusate containing an erythropoietin in accordance with the present invention. Minimal deterioration of organ function occurred during the transport and upon implant and reperfusion of the organs in situ.
>
> In another embodiment of the invention, a surgical procedure to repair a heart valve required temporary cardioplegia and arterial occlusion. Prior to surgery, the patient was infused with 500 U erythropoietin per kg body weight. Such treatment prevented hypoxic ischemic cellular damage, particularly after reperfusion.

Thus, Brines' et al. teach a method for which EPO is used to treat or prevent ischemia in an organ recipient who is at risk of suffering an ischemic event after an organ transplant has occurred, which anticipates or makes obvious addresses claims 17, 19-21 and 23). It is known in the art that when an organ is transplanted, that an ischemic event can occur when reperfusion, or blood flow, is recommenced. However, as Brines et al. teach, when the organs are exposed to EPO, either by perfusing the organ in an EPO solution or by bathing the organ in an EPO solution, this will lessen or reduce the risk of ischemic injury to transplanted organ and hence to the patient receiving the donated organ. It can be concluded that the organs were exposed to the EPO solution for a time sufficient to reduce the effects of ischemia in a patient, and at a concentration equal to that stated in claim 19 of the instant application. Thus, inherently, if the concentration is equivalent, the result is equivalent in both instances.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Mayer, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 8.30am to 5.00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SMM
08 September 2005

JON WEBER
SUPERVISORY PATENT EXAMINER